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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,485	HANADA ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-3,5,7,8,14,25-28,31,37-39 and 42-48 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-3,5,7,8,14,25-28,31,37-39 and 42-48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1, 2, 5, 7, 8, 14, 25-28 and 31 have been amended. Claims 4, 6, 9-13, 15-24, 29, 30, 32-36, 40 and 41 have been canceled. Claims 42-48 have been added. Claims 1-3, 5, 7, 8, 14, 25-28, 31, 37-39, 42-48 are pending and under consideration.

2. Applicant has responded to the restriction requirement of March 21, 2005 by amending the claims to the single invention of Group I (M.P.E.P. 818.02(c)) . Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Numerous references are of record in the file. However, a 1449 form which would allow the examiner to considering each of said references is missing from the file. Applicant is invited to replace any missing IDS form.

Specification

4. The Brief Description of Figure 6 is objected to for failing to conform to the Sequence Rules, because the appropriate Sequence Identifiers are not incorporated into the description. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 5, 7, 8, 14, 25, 26, 28, 31, 42-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 recites "stimulating an immune response to FGF-5 that decreases FGF-5 expression or activity to stimulate a cytotoxic T cell response of cells of the neoplasm". It is unclear if decrease in the expression or activity of FGF-5 is required for the stimulation of the

CTL response; it is unclear if "the cells of the neoplasm" such as TIL, are the only cells being referred to the stimulation of the CTL response because the wording of the claim states "CTL response of cells of the neoplasm" rather than ---CTL response to cells of the neoplasm". Amendment of the claim to the text of claim 1 in provisional application 60/157,103 will overcome this rejection.

(B) Claim 5 is dependent upon a canceled claim. For purpose of examination, claim 5 will be read as being dependent on claim 1.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5, 7, 8, 14, 25, 26, 28, 31 and 42-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

(A)Claim 1 has been amended to recite stimulating an immune response to FGF-5 that decreases FGF-5 expression or activity to stimulate a cytotoxic T cell response of cells of the neoplasm. The specification as filed contemplates modulating an immune response or modulating FGF-5 expression or activity (page 3, line 34 to page 4, line 1), where modulates encompasses either an increase or a decrease. The specification contemplates the administration of an FGF-5 polypeptide or T-cells activated by an FGF-5 polypeptide as a means of stimulating an immune response (page 4, lines 6-11). The specification teaches means of decreasing the expression or activity of FGF-5 by administration of FGF-5 anti-sense nucleic acids or FGF-5 binding molecules (page 5, lines 17-24). Stimulating an immune response against FGF-5 and decreasing the expression or activity of FGF-5 are two different methods as originally contemplated by the specification, thus the specification and claims as filed fails to provide support for claim 1, which is a single method which both stimulates the immune response and

decreases the expression or activity of FGF-5. One of skill in the art would reasonably conclude that applicant was not in possession of the invention at the time of filing. Amendment of the claim to the text of claim 1 in provisional application 60/157,103 will overcome this rejection.

(B)Claim 48 embodies the method of claim 47 wherein the immunogenic fragment stimulates an immune response that is therapeutically immunogenic in HLA-A2+ individuals. The specification as filed states on page 26 that "other epitopes within the FGF-5 peptide may be immunogenic for individuals who are not HLA-A3+ (for example, HLA-A2+ subjects, who constitute about 50% of the Caucasian population)". The speculation that an amino acid sequence having 8-12 residues of SEQ ID NO:4, 6, 8, 10 or 12 would possible provide an immunogenic epitope to HLA-A2+ individuals does not provide support for the instant claim 42 which requires a therapeutic immune response. IT is noted that the specification describes SEQ ID NO:19 as comprising the epitope of FGF-5 for HLA-A3+ individuals. The disclosure of SEQ ID NO:19 does not adequately describe the claimed genus of immunogenic fragments because the genus tolerates members which are highly variant ins structure from SEQ ID NO:19 because the only structural requirement for membership in this genus is to minimally comprise 8-12 residues of SEQ ID NO:6. One of skill in the art would reasonable conclude that applicant was not in possession of the invention of claim 48 at the time of filing.

9. Claims 1-3, 5, 7, 8, 14, 25-28, 31, 37-39, 42-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized by In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is

needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-3, 5, 7, 8, 14, 25-28, 31 and 42-48 are drawn to a method of treating a subject comprising administering an FGF-5 polypeptide to said subject. Claims 37-39 are drawn to a method of lysing a cell of a neoplasm in a subject comprising administering an FGF-5 polypeptide to said subject. The term FGF-5 polypeptide encompasses disclosed sequences of FGF-5 such as SEQ ID NO:6, 18 and 19, as well as variants of said sequences. Thus all claims require the treatment of a subject having a neoplasm expressing FGF-5, and a subset of claims requires treatment by variants of FGF-5 which are speculated upon by the specification, but not disclosed (pages 32-38). The specification teaches that an isolated T-cell clone 2 which was isolated from a regressing metastatic lesion from a renal cell carcinoma (page 23, lines 18-23). The specification teaches that said clone 2 recognized an antigen shared between renal cell carcinomas, and that this recognition was restricted to HLA-A3+ (page 24, lines 7-25). The specification also teaches that the Clone 2 CTL response was directed to a non-mutated epitope within the FGF-5 (page 26, lines 7-13). The specification does not provide objective evidence that a Clone 2 CTL response can be generated in vivo which would actively lyse FGF-5 expressing tumor cells in vivo.

The art teaches that administration of a tumor associated peptide can generate a quantifiable CTL in the peripheral blood of cancer patients, such a CTL response is not associated with clinical evidence of tumor regression (Lee et al, Journal of Immunology, 1999, Vol. 163, pp. 6292-6300). Further, Ohlen et al (Journal of Immunology, 2001, Vol.166, pp. 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995, Vol. 7, pp. 715-725) teach that T-cells which are impaired in

the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). These references serve to demonstrate that the lysis or "recognition" of target cells expressing a FGF-5 antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that a T-cell clone is able to recognize tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro. Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998, vol. 4, pp. 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In pre-clinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that

the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion". In support of these conclusions Jager et al (PNAS, 2000, Vol. 97, pp. 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of a anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993, Vol. 7, pp. 99-105 and the abstract of Algarra et al, International Journal of Clinical and Laboratory Research, 1997, Vol. 27, pp. 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, Bodey et al (Anticancer Research, 2000 Jul-Aug, Vol. 20, pp. 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Further, the instant claims encompass methods reliant upon fragments and variants of FGF-5. The specification teaches that SEQ ID NO:6 is a target of the Clone 2 CTL which recognizes SEQ ID NO:6 in the context of HLA-A3+. The specification does not provide objective evidence that a fragment of FGF-5 is the target for any other CTL which recognizes FGF-5 in the context of a non-HLA-A3+ context. The art teaches that MHA/peptide binding

predictions are not sufficient for identifying CD8 T cell epitopes (Pelte et al, Journal of Immunology, 2004, Vol. 172, pp. 6783-6789). There is no nexus between the recognition of FGF-5 in the context of HLA-A3+ and the recognition of FGF-5 in the context of non-HLA-A3+, thus one cannot reliably construe that FGF-5 on the surface of a tumor cell would be a target for a non-HLA-A3+ restricted T-cell. The specification does not teach how to make variants of FGF-5 that would function in a method of treating a subject, thus one of skill in the art would be subject to yet another degree of undue experimentation in order to practice the broadly claimed invention.

Due to the unreliability of the art as discussed above, the lack of a working example which demonstrates the successful treatment of a subject with an FGF-5 expressing tumor, and the breath of the claims as including variants and numerous fragments of FGF-5, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.

7/25/2005

Karen A. Canella

KAREN A. CANELLA PH.D
PRIMARY EXAMINER